REMARKS

Entry of the foregoing amendments and reconsideration of the subject application as amended pursuant to and consistent with 37 C.F.R. § 1.111, in light of the remarks which follow, is respectfully requested.

1. Status of the Claims

Upon entry of the foregoing amendment claims 17-32 are pending. Claims 1-16 and 33-48 were previously canceled without prejudice or disclaimer of the subject matter therein. Applicants reserve the right to file one or more continuation or divisional applications directed to the cancelled subject matter.

Claims 17, 21, 25, 29, 30,31, and 32 are newly amended herein. Support for the claim amendment "isolated away from nonadherent cells in bone marrow" is found, for example, on p. 6, lines 11-15 and p. 15, lines 7-12. Support for the claim amendment "one hour to a year" is found, for example, on p. 9, lines 7-13. Support for the claim amendment "wherein donor DNA from said isolated bone marrow stromal cells is not detected in the bone marrow in the rescued mammal after administration" is found, for example, p. 22, lines 20-24.

The amendments are not believed to add new matter and entry is respectfully requested.

2. Rejection of claims 17-32 under 35 U.S.C. § 112, second paragraph

At page 2 of the Office Action, the Examiner rejects claims 17-32 under 35 U.S.C. § 112, second paragraph, allegedly for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection is respectfully traversed.

At page 3 of the Office Action, independent claims 17, 21, 25, and 29-32 are rejected because "[i]t is unclear how the cells may be administered immediately upon isolation and further be short-term cultured cells."

In reply, claims 17, 21, 25, and 29-32 have been amended to delete the phrase "short-term cultured cells." The amendments to the independent claims are believed to render the rejection moot. Therefore, the rejection of dependent claims 18-20, 22-24, 26-

28 is also rendered moot. Reconsideration and withdrawal of the rejection is respectfully requested.

3. Rejection of claims 17-32 under 35 U.S.C. § 112, first paragraph ("new matter")

At page 4 of the Office Action, the Examiner rejects claims 17-32 under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to convey the inventors had possession of the claimed invention. The rejection is respectfully traversed.

At page 4 of the Office Action, the Examiner discusses the phrase "short-term cultured cells" and argues that the specification fails to provide evidence Applicants were in possession of such a genera of all short-term culture marrow stromal cells. However, claims 17, 21, 25, 29, 30, 31, and 32 as amended no longer recite the phrase "short term cultured cells." The amendments to the claims are believed to overcome the rejection. Reconsideration and withdrawal of the rejection is respectfully requested.

4. Claim interpretation comment

At the top of page 7 of the Office Action, the Examiner has stated that "Applicant's claims are not limited to only administration of the marrow stromal cells, but the composition compris[ing] isolated marrow stromal cells." The Examiner has asserted a similar stance in the art rejections, thereby applying art teaching transplantation of bone marrow, that is, all the components of bone marrow.

Applicants respectfully point out that the claims do *not* recite a composition comprising isolated marrow stromal cells. Rather, the claims recite the step of "administering isolated bone marrow stromal cells from an allogenic donor mammal."

As disclosed in the specification, bone marrow stromal cells are isolated from other cells in the bone marrow by their ability to adhere to plastic dishes. See, for instance, p. 6, lines 11-15 and p. 15, lines 7-12. It is well known in the art that hematopoietic stem cells are non-adherent cells. Thus, the disclosure clearly teaches separating bone marrow stromal cells from non-adherent cells, including hematopoietic stem cells, to produce the isolated bone marrow stromal cells. While the specification is

clear in the meaning of "isolated bone marrow stromal cells," to recite this aspect more distinctly, the claims have been amended to recite that the isolated bone marrow stromal cells are "isolated away from nonadherent cells in bone marrow."

While the claims do recite "said method comprising," which is considered "open" claim language, it is open with regard to *additional method steps*. See MPEP 2111.03: "The transistion "comprising" in a method claim indicates that the claim is open-ended and allows for additional steps" (citing *Invitrogen Corp. v. Biocrest Mfg.*, L/P., 327 F.3d 1364, 1368, 66 USPQ2s 1631, 1634 (Fed. Cir.2003).

Applicants respectfully urge the Examiner to construe the claims accordingly.

5. Rejection of claims 17-32 under 35 U.S.C. § 102(b)

At page 7 of the Office Action, the Examiner rejected claims 17-32 under 35 U.S.C. § 102(b) as being anticipated by Remes et al. (Remes, et al., Ann. Med. 28: 79-81 (1996)) ["Remes"]. The rejection is respectfully traversed.

The Examiner argues "with regard to each method" that Remes teaches it was well known in the art to administer bone marrow, isolated from a patient and which inherently comprises bone marrow stromal cells to a patient, administration of the cells by infusion and that such methods are used to treat humans. The Examiner argues, *inter alia*, that it was also well known in the art to administer bone marrow to treat ablated bone marrow, chemotherapeutically ablated marrow and TBI-ablated marrow.

However, claim 17, as amended, recites the phrase "*in vitro* culturing for one hour to a year and wherein donor DNA from said isolated bone marrow stromal cells is not detected in the bone marrow in the rescued mammal after administration." Claims 21, 25, 29, 30, 31, and 32 have been similarly amended. Thus, the teachings of Remes must be reconsidered in view of the amendments to the claims.

As the Examiner is aware, for prior art to be anticipatory under section 102, the Federal Circuit has held that each and every element of the claimed invention must be disclosed in a single item of prior art in the form literally defined in the claim. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 213 U.S.P.Q. 81, 90 (Fed. Cir. 1986). First of all, Remes does not disclose or suggest the administration of *isolated* bone marrow stromal cells. Indeed, Remes is completely silent regarding bone marrow

stromal cells. Remes discusses hematopoietic stem cells and their use in bone marrow transplantation, autologous stem cell transplantation and autologous blood cell transplantation. Remes discusses the "rapid and sustained engraftment" that can be achieved with the latter. Indeed, successful engraftment of donor cells is the implicit goal of all of the transplantation therapies Remes discusses. Remes fails to teach administration of isolated bone marrow stromal cells, for instance, to rescue a mammal from a lethal dose of total body irradiation, wherein the administered cells do not engraft in the so-rescued mammal. Engraftment of allogeneic donor cells can be assessed by detection of donor DNA in recipient tissue, for instance, bone marrow. Thus, the recitation of "wherein donor DNA from said isolated bone marrow stromal cells is not detected in the bone marrow in the rescued mammal after administration" distinguishes the claimed methods from art teaching donor cell engraftment.

Because Remes fails to teach each and every element of the claims, the Examiner's *prima facie* case of anticipation is legally deficient. Reconsideration and withdrawal of the rejection is respectfully requested.

6. Rejection of claims 17-32 under 35 U.S.C. § 103

At page 8 of the Office Action, the Examiner rejected claims 17-32 under 35 U.S.C. § 103 as being unpatentable over Anklesaria '87 and further in view of U.S. Patent No. 5,635,386 (Palsson) ['386] as further evidenced by Shpall (Shpall et al., Ann. Rev. Med. 48: 241-251 (1997) ["Shpall"]; Remes (Remes, et al., Ann. Med. 28: 79-81 (1996)) ["Remes"]; Werts (Werts et al., Radiation Research 81: 20-30 (1980) ["Werts"]; and Piersma (Piersma et al., Brit. J. Haematology 4: 285-290 (1983)) ["Piersma"].

The rejection is respectfully traversed. The teachings of Anklesaria, Palsson, Shpall, Remes, Werts and Piersma must be reconsidered in view of the amendments to the claims.

It is noted that while Werts et al. ((1980) Radiation Research 81:20-30) was cited in the opening statement of the rejection, the Examiner has not mentioned Werts anywhere in the body of the rejection. Furthermore, a copy of the Werts reference was not provided by the Examiner. Therefore, Applicants do not further address the Werts reference as it is unknown to Applicants why Werts is cited by the Examiner.

Anklesaria discloses administration of clonal stromal cells (GB1/6 or GB1neo^r) to irradiated mice. Several lines of evidence indicate that the donor cells engrafted in the recipients' bone marrow. See, for instance, p. 7682, Table 1, p. 7683, Figure 2, top panel and p. 7684, Discussion, first paragraph. Anklesaria clearly teaches that engraftment of the donor cells is directly related to the stimulation of hematopoietic recovery. For instance, Anklesaria conclude that their "data revealed evidence for stimulation of hematopoietic recovery in vivo in stromal cell line-engrafted mice" (p. 7685, left column, third full paragraph). In the Abstract, it is stated that "engrafted mice demonstrated donor-originating Glu6*P*I-a$^+$ stromal cells in marrow sinuses in situ 2 mo after transplantation and a significantly enhanced hematopoeitic recovery compared with control irradiated nontransplanted mice." Thus, Anklesaria does not teach or suggest that a method of administering isolated bone marrow stromal cells from an allogenic donor mammal to a recipient, wherein the donor cells do not engraft in the recipient bone marrow, would enhance hematopoietic recovery in the recipient.

None of Palsson, Shpall, Remes, or Piersma, individually or in combination, overcome the deficiencies of Anklesaria.

Palsson teaches methods of culturing human hematopoietic stem cells in vitro that permit expansion of the hematopoietic stem cells, which, Palsson teach, is helpful for therapeutic methods using hematopoietic stem cells. These cultures of hematopoietic stem cells may or may not contain bone marrow stromal cells (col. 10, lines 29-30). That is, the hematopoietic stem cells may be isolated away from bone marrow stromal cells, however, Palsson does not teach or suggest bone marrow stromal cells isolated away from hematopoietic stem cells. Furthermore, Palsson does not teach or suggest administering isolated bone marrow stromal cells in a therapeutic method. Therefore, Palsson cannot teach or suggest administering isolated bone marrow stromal cells, wherein the donor cells do not engraft in the recipient bone marrow, resulting in enhanced hematopoietic recovery.

Shpall is an overview of the use of peripheral blood stem cells for autologous transplants. Engraftment of the "donor" cells is discussed. See p. 242 "The Leukapheresis Procedure" and p. 247, "Purification of Peripheral Blood Progenitors." As mentioned previously with regard to Remes, successful engraftment of donor cells is

the implicit goal of all transplantation therapies. Shpall does not mention bone marrow stromal cells at all. Therefore, Shpall cannot teach or suggest isolated bone marrow stromal cells. Accordingly, Shpall cannot and does not teach or suggest administering isolated bone marrow stromal cells to assist in hematopoietic recovery after radiation or chemotherapeutic marrow damage, wherein the administered stromal cells do not engraft.

Remes, as discussed previously, does not disclose or suggest the administration of isolated bone marrow stromal cells and is completely silent regarding bone marrow *stromal* cells. Remes discusses the "rapid and sustained engraftment" that can be achieved with the autologous blood cell transplantation. As noted before, successful engraftment of donor cells is the implicit goal of all of the transplantation therapies discussed in Remes. Remes fails to teach administration of isolated bone marrow stromal cells, for instance to rescue a mammal from a lethal dose of total body irradiation, wherein the administered cells do not engraft in the so-rescued mammal.

Piersma teaches transplantation of donor bone marrow, which comprises stromal cells (CFU-F) and other bone marrow cells including nonadherent cells, to lethally-irradiated mice. Stromal cells of the donor bone marrow engrafted in the recipient mice. See, for instance, p. 285 Summary and p. 288, Table 1. Piersma, however, does not teach or suggest *isolated* bone marrow stromal cells or the administration of the same to rescue a mammal from a lethal dose of total body irradiation. The teachings in Piersma implicitly teach the positive correlation between stromal cell engraftment and marrow stroma reestablishment. Consequently, Piersma does not teach or suggest that administration of isolated bone marrow stromal cells, wherein the administered cells do not engraft in the rescued mammal, would contribute to hematopoietic recovery.

In summary, Anklesaria does not teach or suggest that a method of administering isolated bone marrow stromal cells from an allogenic donor mammal to a recipient, wherein the donor cells do not engraft in the recipient bone marrow, would be successful in enhancing hematopoietic recovery in the recipient. Based on the teachings of Anklesaria, one of ordinary skill in the art would not expect enhanced hematopoietic recovery in the absence of engraftment of the donor cells in the recipient. Furthermore, none of the other references (Palsson, Shpall, Remes and Piersma) cited provides a reasonable expectation of enhanced hematopoietic recovery in the absence of

engraftment of the donor cells. Thus, the deficiencies of Anklesaria are not overcome by the other references, individually or in any combination.

Applicants have discovered that administration of isolated bone marrow stromal cells immediately after isolation or with limited in vitro culturing unexpectedly enhances endogenous hematopoiesis *without engraftment* of the administered stromal cells. As stated in MPEP 716.02(s), absence of an expected property, such as engraftment of donor cells to enhance hematopoiesis, is evidence of non-obviousness.

Accordingly, the claimed invention is not obvious in view of the teachings of Anklesaria, Palsson, Shpall, Remes, or Piersma, individually or in any combination. Reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In conclusion, this amendment and reply is believed to be a full response to the outstanding Office Action. Should any issues remain outstanding or if there are any questions concerning this paper, or the application in general, the Examiner is invited to telephone the undersigned representative at the Examiner's earliest convenience.

EXCEPT for issue fees payable under 37 C.F.R. § 1.18, the Commissioner is hereby authorized by this paper to charge any additional fees during the entire pendency of this application including fees due under 37 C.F.R. §§ 1.16 and 1.17 which may be required, including any required extension of time fees, and Notice of Appeal fees, or credit any overpayment to Deposit Account No. 50-0573. This paragraph is intended to be a **CONSTRUCTIVE PETITION FOR EXTENSION OF TIME** in accordance with 37 C.F.R. § 1.136(a)(3).

Respectfully submitted,

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